

SUBSTITUTED HETEROARYL AND HETEROCYCLIC COMPOUNDS USEFUL IN TREATING INFLAMMATORY DISORDERS

FIELD OF THE INVENTION

This invention relates to a series of substituted heteroaryl and heterocyclic
5 compounds, pharmaceutical compositions and methods for use thereof in treating
or ameliorating an inflammatory disorder. More particularly, the substituted
heteroaryl and heterocyclic compounds of the present invention are nicotinamide
adenine dinucleotide oxidase hydride donor inhibitors and are useful in treating or
ameliorating a reactive oxygen species mediated inflammatory disorder.

10 BACKGROUND OF THE INVENTION

The nicotinamide adenine dinucleotides (NAD, NADH, NADP and NADPH)
are essential cofactors in all living systems and function as hydride acceptors
(NAD, NADP) and hydride donors (NADH, NADPH) in biochemical redox
reactions. The six-step biosynthetic pathway begins with the oxidation of
15 aspartate to iminosuccinic acid, which is then condensed with dihydroxyacetone
phosphate to give quinolinic acid. Phosphoribosylation and decarboxylation of
quinolinic acid gives nicotinic acid mononucleotide. Adenylation of this
mononucleotide followed by amide formation completes the biosynthesis of NAD.
An additional phosphorylation gives NADP (Begley, TP., et al., The Biosynthesis of
20 Nicotinamide Adenine Dinucleotides in Bacteria, *Vitam. Horm.*, **2001**, 61, 103-
119).

The importance of reactive oxygen species (ROS) in the pathogenesis of
inflammatory diseases is increasingly recognized. During inflammation,
polymorphonuclear leucocytes (PMN) and macrophages become stimulated by
25 lipopolysaccharide (LPS) and tumor necrosis factor alpha (TNF- α) as well as
cytokines IFN- γ and interleukin-2 (IL-2). Stimulation results in the cellular

assembly of a nicotinamide adenine dinucleotide oxidase hydride donor, in particular NADPH, a membrane bound enzyme which is the major source of ROS. The generation of ROS has been shown to be elevated up to 10 fold in patients with various inflammatory and autoimmune rheumatic diseases (R. Miesel, et al.,
 5 Suppression of Inflammatory Arthritis by Simultaneous Inhibition of Nitric Oxide Synthase and NADPH Oxidase, *Free Radical Biology & Medicine*, **1996**, 20(3), 75-81).

Two known inhibitors of NADPH Oxidase, diphenylene iodoniumchloride (DPI) and staurosporine have been shown to have antiinflammatory effects in mice
 10 with potassium peroxochromate arthritis. Daily doses of 2.8 μ mol/kg of DPI and 30 nmol/kg staurosporine inhibited the arthritis by 50%. Complete inhibition was obtained with 10 mmol/kg DPI while 85% inhibition of the arthritis was achieved with 100 nmol staurosporine (R. Miesel, et al., Antiinflammatory Effects of NADPH Oxidase Inhibitors, *Inflammation*, **1995**, 19(3), 347-362).

15 The antirheumatic drug Piroxicam has been shown to reduce levels of ROS in human patients with rheumatoid arthritis and osteoarthritis by 25% at pharmacological doses. *In vitro* studies showed that this inhibition was caused by interference of the activation of NADPH Oxidase (P. Biemond, et al., Superoxide Production by Polymorphonuclear Leucocytes in Rheumatoid Arthritis and
 20 Osteoarthritis: In vivo Inhibition by the Antirheumatic Drug Piroxicam Due to the Interference With the Activation of the NADPH Oxidase, *Annals of the Rheumatic Diseases*, **1986**, 45, 249-255).

The deposition of β -amyloid in the brain is the key pathogenic event in Alzheimer's disease. Recently, β -amyloid has been shown to induce the
 25 stimulation of NADPH oxidase in human neutrophils and microglia in a dose dependent manner. The subsequent production of ROS is at least in part responsible for the neurodegenerative effects of β -amyloid (V. D. Bianca, et al., β -

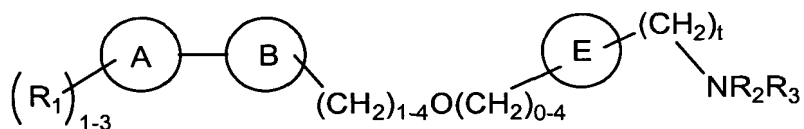
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Amyloid Activates the O₂-Forming NADPH Oxidase in Microglia, Monocytes, and Neutrophils, *The Journal of Biological Chemistry*, **1999**, 274, 15493-15499).

The object of the present invention is to provide substituted heteroaryl and heterocyclic compounds as nicotinamide adenine dinucleotide oxidase hydride donor inhibitors and a method for use of such compounds in treating or ameliorating a reactive oxygen species mediated inflammatory disorder.

SUMMARY OF THE INVENTION

The present invention relates to substituted heteroaryl and heterocyclic compounds of Formula (I):



Formula (I)

10 wherein:

B is heteroarylene; wherein heteroarylene is selected from an aromatic monocyclic ring having five members of which at least one member is a N, O or S atom and which optionally contains one additional N atom;

A and E are independently phenylene or pyridinylene;

15 t is an integer from 1 to 4;

R₁ is selected from hydrogen, C₁₋₈alkyl, C₁₋₈alkoxy, NH₂, NH(C₁₋₈alkyl), N(C₁₋₈alkyl)₂, halogen or hydroxy; wherein R₁ is substituted on the 3, 4 or 5 position of the "A" ring;

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R₂ and R₃ are independently selected from hydrogen, C₁₋₈alkyl-R₄ or C₃₋₆cycloalkyl;

R₄ is selected from (C₁₋₈)alkoxy, NH₂, NH(C₁₋₈alkyl), N(C₁₋₈alkyl)₂, (halo)₁₋₃, hydroxy, C₃₋₆cycloalkyl-R₅, heterocyclyl-R₅, aryl-R₅ or heteroaryl-R₅; and,

- 5 R₅ is 1 to 2 substituents selected from hydrogen, C₁₋₈alkyl or (C₁₋₈)alkoxy (wherein alkoxy is substituted on a carbon atom);

and pharmaceutically acceptable salts thereof.

The present invention also provides a method for treating or ameliorating a reactive oxygen species mediated inflammatory disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound selected from Formula (I).

In a preferred embodiment of the method of the present invention, the reactive oxygen species is selected from the group consisting of superoxide, hydrogen peroxide, hydroxyl radical and HOCl.

15 DETAILED DESCRIPTION OF THE INVENTION

Aspects of the present invention include compounds of Formula (I) wherein B is selected from oxazolylene, thiazolylene, imidazolylene, pyrimidinylene, pyrazinylene or triazinylene.

Another aspect of the present invention includes compounds of Formula (I) wherein B is selected from oxazolylene, thiazolylene or imidazolylene.

Aspects of the present invention include compounds of Formula (I) wherein t is an integer from 1 to 2.

Another aspect of the present invention includes compounds of Formula (I) wherein t is an integer 1.

Aspects of the present invention include compounds of Formula (I) wherein R₁ is selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, NH₂, NH(C₁₋₄alkyl),
5 N(C₁₋₄alkyl)₂, halogen or hydroxy; wherein R₁ is substituted on the 3, 4 or 5 position of the "A" ring.

Another aspect of the present invention includes compounds of Formula (I) wherein R₁ is selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy or halogen; wherein R₁ is substituted on the 4 position of the "A" ring.

10 Aspects of the present invention include compounds of Formula (I) wherein R₂ and R₃ are independently selected from hydrogen, C₁₋₄alkyl-R₄ or C₃₋₆cycloalkyl.

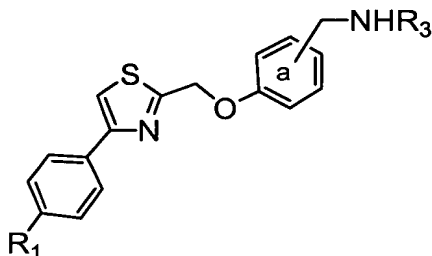
Aspects of the present invention include compounds of Formula (I) wherein R₄ is selected from C₁₋₄alkoxy, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)₂, (halo)₁₋₃, hydroxy,
15 C₃₋₆cycloalkyl-R₅, heterocyclyl-R₅, aryl-R₅ or heteroaryl-R₅.

Another aspect of the present invention includes compounds of Formula (I) wherein R₄ is selected from heterocyclyl-R₅ or heteroaryl-R₅.

Another aspect of the present invention includes compounds of Formula (I)
20 wherein R₄ is selected from pyrrolidiny-R₅, morpholinyl-R₅, furyl-R₅ or indolyl-R₅.

Aspects of the present invention include compounds of Formula (I) wherein R₅ is 1 to 2 substituents selected from hydrogen, C₁₋₄alkyl or (C₁₋₄)alkoxy (wherein alkoxy is substituted on a carbon atom).

Exemplifying the invention is a compound of Formula (I) selected from a compound of Formula (Ia)



Formula (Ia)

wherein R_1 , the position "a" and R_3 are dependently selected from:

Cpd	R_1	a	R_3	
1	Cl,	3	and	n-propyl;
1a	Cl,	4	and	n-propyl;
2	Cl,	3	and	isobutyl;
3	Cl,	3	and	cyclopentyl;
4	Cl,	3	and	cyclohexyl;
5	Cl,	3	and	cyclopropyl;
6	Cl,	3	and	CH_2 -(1-Me)-2-pyrrolidinyl;
7	Cl,	3	and	$(\text{CH}_2)_2$ -4-morpholinyl;
8	Cl,	3	and	(5-Me)furfuryl;
9	Cl,	3	and	$(\text{CH}_2)_2$ -(5-OMe)-1 <i>H</i> -indol-3-yl;
10	Cl,	4	and	cyclopentyl;
	or			
11	Cl,	3	and	H.

- The compounds of the present invention may also be present in the form of
- 5 pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts" (*Ref. International J. Pharm.*, **1986**, 33, 201-217; *J. Pharm.Sci.*, **1997** (Jan), 66, 1, 1). Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts.
- 10 Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic,

propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pantoic, 2-naphthalenesulfonic, *p*-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases
5 include, but are not limited to, basic or cationic salts such as benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the
10 compounds which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after
15 administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or
20 reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent
25 stage using methods known in the art.

Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or

common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

The term "independently" means that when a group is substituted with more than one substituent that the substituents may be the same or different. The term
5 "dependently" means that the substituents are specified in an indicated combination of structure variables.

Unless specified otherwise, the term "alkyl" refers to a saturated straight or branched chain typically consisting solely of 1-8 hydrogen substituted carbon atoms, 1-6 hydrogen substituted carbon atoms or 1-4 hydrogen substituted carbon
10 atoms. The term " (C_{a-b}) " (where a and b are integers) refers to an alkyl chain containing from a to b carbon atoms inclusive. Accordingly, (C_{1-4}) alkyl denotes an alkyl chain containing 1, 2, 3 or 4 carbon atoms. Alkyl chains are optionally substituted within the alkyl chain or on a terminal carbon atom. The term " (C_{a-b})
alkylene" refers to an alkyl group functioning as a linking group.

15 The term " (C_{a-b}) alkoxy" refers to $-O-(C_{a-b})$ alkyl, where alkyl is as previously defined.

The term " (C_{a-b}) cycloalkyl" refers to a saturated or partially unsaturated monocyclic alkyl ring consisting of 3-8 hydrogen substituted carbon atoms or a
20 saturated or partially unsaturated bicyclic ring consisting of 9 or 10 hydrogen substituted carbon atoms. Examples include, and are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. The term "cycloalkylene" refers to a cycloalkyl group functioning as a linking group.

The term "heterocyclyl" refers to a saturated or partially unsaturated ring
25 having five members of which at least one member is a N, O or S atom and which optionally contains one additional O atom or one additional N atom, wherein at most two nitrogen atoms are adjacent; a saturated or partially unsaturated ring

having six members of which one, two or three members are a N atom, wherein at most two nitrogen atoms are adjacent; or, a saturated or partially unsaturated bicyclic ring having nine or ten members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms, wherein at most two nitrogen atoms are adjacent. Examples include, and are not limited to, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl or piperazinyl. The term "heterocyclylene" refers to a heterocyclyl group functioning as a linking group.

The term "aryl" refers to an aromatic monocyclic ring containing 6 hydrogen substituted carbon atoms, an aromatic bicyclic ring system containing 10 hydrogen substituted carbon atoms or an aromatic tricyclic ring system containing 14 hydrogen substituted carbon atoms. Examples include, and are not limited to, phenyl, naphthalenyl or anthracenyl. The term "arylene" refers to an aryl group functioning as a linking group.

The term "heteroaryl" refers to an aromatic monocyclic ring system containing five members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms, wherein at most two nitrogen atoms are adjacent; an aromatic monocyclic ring having six members of which one, two or three members are a N atom, wherein at most two nitrogen atoms are adjacent; an aromatic bicyclic ring having nine members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms, wherein at most two nitrogen atoms are adjacent; an aromatic bicyclic ring having ten members of which one, two or three members are a N atom, wherein at most two nitrogen atoms are adjacent; or, an aromatic tricyclic ring system containing 13 or 14 members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms, wherein at most two nitrogen atoms are adjacent. Examples include, and are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl,

isoxazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyrazinyl and triazinyl. The term "heteroarylene" refers to a heteroaryl group functioning as a linking group.

An embodiment of the present invention includes the use of a compound of Formula (I) for the preparation of a pharmaceutical composition or medicament thereof for treating or ameliorating a reactive oxygen species mediated inflammatory disorder in a subject in need thereof.

An embodiment of the present invention includes a method for treating or ameliorating a reactive oxygen species mediated inflammatory disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an instant compound or pharmaceutical composition thereof.

In a method for treating or ameliorating a reactive oxygen species mediated inflammatory disorder, the term "reactive oxygen species" includes, and is not limited to, a reactive oxygen species selected from a superoxide, hydrogen peroxide, hydroxyl radical or HOCl reactive oxygen species.

A reactive oxygen species mediated inflammatory disorder includes, and is not limited to, phosphorylation mediated disorders, polymorphonuclear leucocyte mediated disorders, macrophage mediated disorders, lipopolysaccharide mediated disorders, tumor necrosis factor- α mediated disorders, cytokine IFN- γ mediated disorders, interleukin-2 mediated disorders, inflammatory arthritis, potassium peroxochromate arthritis, rheumatoid arthritis, osteoarthritis or Alzheimer's disease.

It is also apparent to one skilled in the art that the therapeutically effective dose for active compounds of the invention or a pharmaceutical composition thereof will vary according to the desired effect. Therefore, optimal dosages to be administered may be readily determined and will vary with the particular compound used, the mode of administration, the strength of the preparation and

the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level.

5 A therapeutically effective amount for use of the instant compounds or a pharmaceutical composition thereof comprises a dose range of from about 0.001 mg to about 1,000 mg, a dose range of from about 0.1 mg to about 500 mg or a dose range of from about 1 mg to about 250 mg of active ingredient per day for an average (70 kg) human.

10 For oral administration, a pharmaceutical composition is preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated.

The terms used in describing the invention are commonly used and known to those skilled in the art. As used herein, the following abbreviations have the indicated meanings:

DEAD	diethylazodicarboxylate
DIBAL	diisobutylaluminum hydride
TPP	triphenylphosphine
mp	melting point
HBSS	
h	Hour
min	Minute
rt	Room temperature

25 General Synthetic Methods

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the schemes that follow. Since the schemes are illustrations,

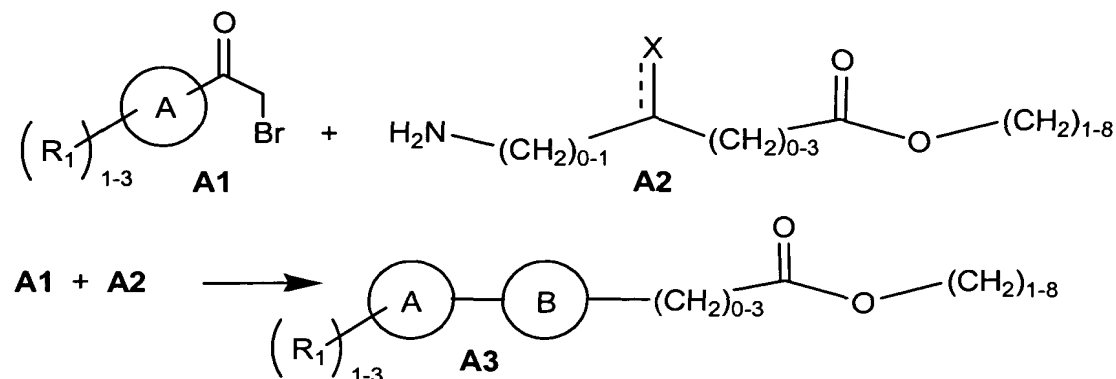
the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

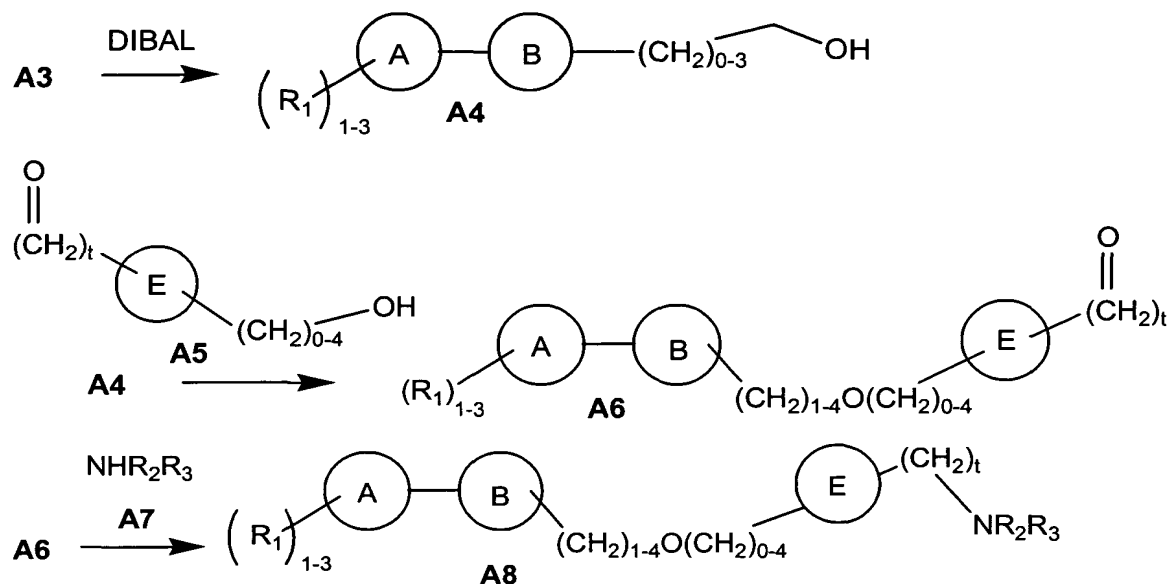
Scheme A

- 5 A bromoacetyl and R_1 substituted "A" ring Compound **A1** can be reacted with an amino and an X heteroatom (wherein X is selected from S, O, NH_2 , $NH(C_{1-8}alkyl)$ or $N(C_{1-8}alkyl)_2$) substituted Compound **A2** in an alcohol such as ethanol to yield an intermediate Compound **A3**. The amino and X heteroatom substituted on
- 10 "B" ring of Compound **A3**; the length of the alkyl chains may be varied as indicated.

- Reduction of the Compound **A3** ester with diisobutyl aluminum hydride gives a hydrolyzed Compound **A4**. A Mitsunobu reaction of Compound **A4** with a hydroxy substituted Compound **A5** (when $(CH_2)_0$) affords an intermediate Compound **A6**
- 15 using coupling reagents such as TPP and DEAD. When Compound **A5** is $(CH_2)_{1-4}$, then the Compound **A4** hydroxy must be converted to a leaving group by either mesylation or halogenation using reagents known to those skilled in the art and the Compound **A5** hydroxy must be converted to an alkoxide base by reaction with a suitable base such as NaH. Reductive amination of the aldehyde
- 20 Compound **A6** with a NHR_2R_3 Compound **A7** gives the target Compound **A8**.

Scheme A

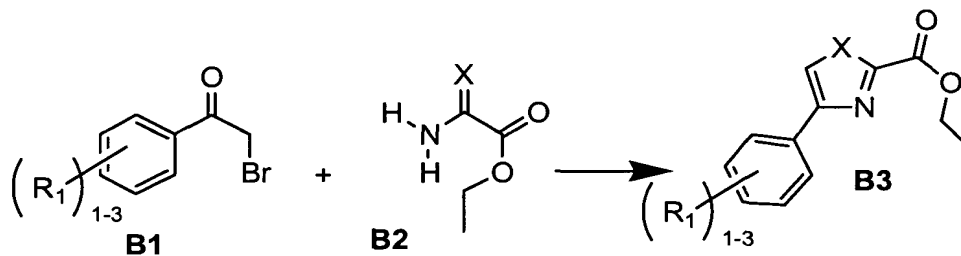


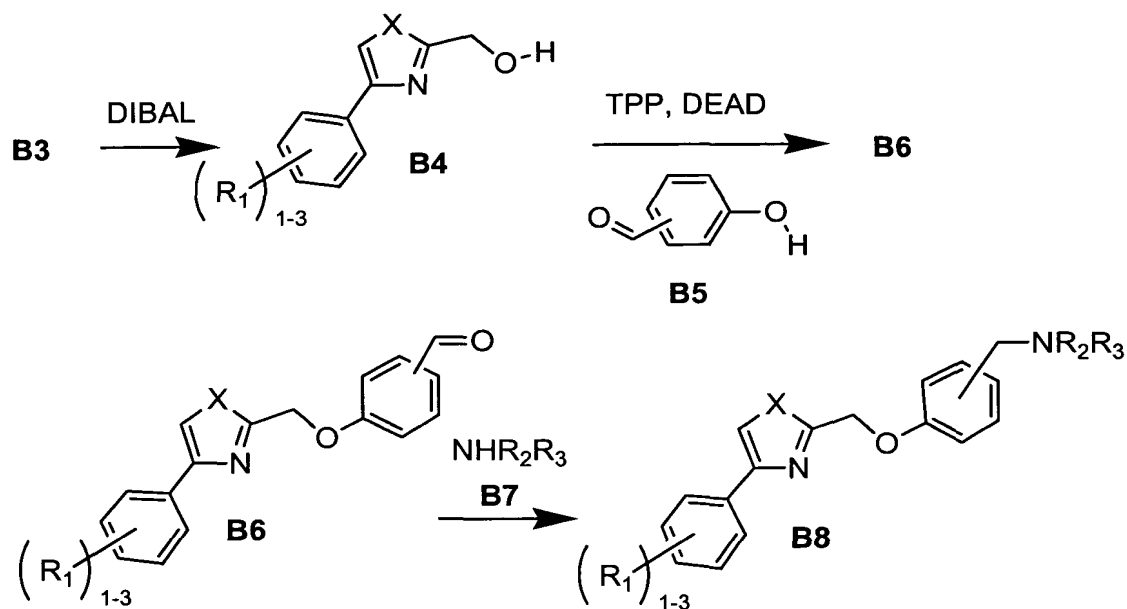


Scheme B

An R_1 substituted bromoacetophenone Compound **B1** can be reacted with an X substituted ethyl oxamate Compound **B2** in an alcohol such as ethanol to yield an intermediate Compound **B3**. Reduction of the ester of Compound **B3** with diisobutyl aluminum hydride gives an alcohol Compound **B4**. Mitsunobu reaction of Compound **B4** with either a 3-hydroxy or 4-hydroxy substituted benzaldehyde Compound **B5** affords a corresponding intermediate Compound **B6**. Reductive amination of the aldehyde Compound **B6** with a substituted amine Compound **B7** gives the target Compound **B8**, wherein the “B” ring comprises 5 members.

Scheme B

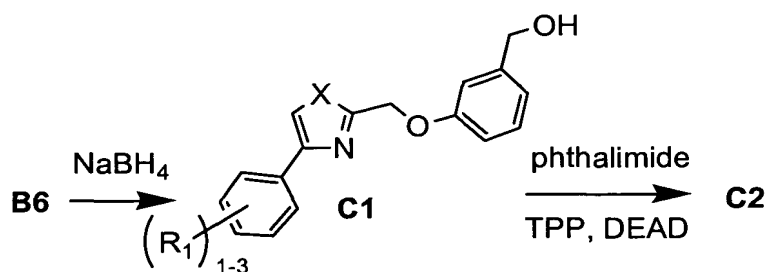


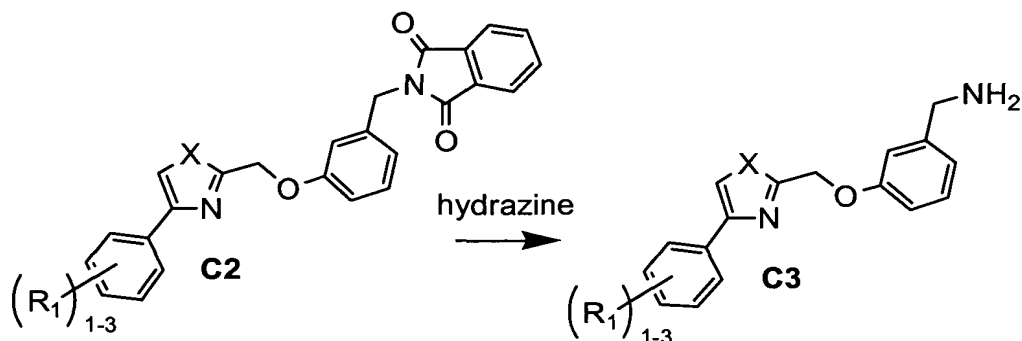


Scheme C

- The aldehyde Compound **B6** from Scheme B is reduced with sodium borohydride to give an alcohol Compound **C1**. A Mitsunobu reaction of Compound **C1** with phthalimide affords an intermediate Compound **C2**. Deprotection of Compound
- 5 **C2** with hydrazine yields the target Compound **C3**, wherein NR_2R_3 is on the 3 position of the phenyl ring.

Scheme C





Specific Synthetic Methods

Specific compounds which are representative of this invention may be prepared as per the following examples offered by way of illustration and not by way of limitation. Also, examples specifically used to prepare intermediates for the further synthesis of compounds of the invention are designated by "Procedure." No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

Example 1

3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]-
N-propyl-benzenemethanamine (Cpd 1)

Following the protocol of Scheme B, a 2-Bromo-4'-chloroacetophenone (3.69 grams) (See Scheme B, Compound **B1**, wherein R_2 is chloro) was dissolved in ethanol (100 mL). Thiooxamate (2.10 grams) (Scheme B, Compound **B2**) and pyridine (1.30 mL) were added to the mixture which was stirred at reflux for 1 hour and then poured into ice-water. The solid was filtered to give an ethyl-2-[4-(4-chlorophenyl)]thiazolylcarboxylate (Scheme B, Compound **B3**). Mp = 102-103 °C; MS 268 (MH^+); 1H NMR ($CDCl_3$) δ 7.87 (d, 2H), 7.75 (s, 1H), 7.43 (d, 2H), 4.52 (q, 2H), 1.47 (t, 3H).

- The carboxylate (6.61 grams) (Scheme B, Compound **B3**) was dissolved in dichloromethane (200 mL) and cooled to -78 °C. A solution of diisobutylaluminum hydride (33 mL, 1.5 M sol'n) was added. The reaction was stirred for 1.5 hours and then warmed to ambient temperature. 1 N aqueous sodium hydroxide (200 mL) was added and the layers were separated. The organic layer was dried over sodium sulfate, concentrated and eluted through a silica gel plug using ethyl acetate as the eluent to give a 2-[4-(4-chlorophenyl)thiazolyl]carbinol (Scheme B, Compound **B4**). Mp 152.5-153.5 °C; MS 226 (MH⁺); ¹HNMR (DMSO) δ 6.15 (t, 1H, OH), 4.80 (d, 2H).
- 10 The carbinol (1.41 grams) (Scheme B, Compound **B4**) was dissolved in tetrahydrofuran (70 mL). 3-hydroxybenzaldehyde (Scheme B, Compound **B5**) (0.76 grams), triphenylphosphine (1.83 grams) and diethylazodicarboxylate (1.10 mL) were added to the mixture which was stirred under nitrogen for 18 hours. Ethyl acetate (50 mL) was then added and the solution was washed with an aqueous 1 N sodium hydroxide solution, followed by water. The organic layer was concentrated and chromatographed on a silica gel column eluted with hexane-ethyl acetate 3:1 to give a 2-(3-formyl)phenoxyethyl-4-(4-chlorophenyl)thiazole (Scheme B, Compound **B6**). Mp 129.5-130 °C ¹HNMR (CDCl₃) δ 10.00 (s, 1H), 5.48 (s, 2H).
- 20 The thiazole (0.31 grams) (Scheme B, Compound **B6**) was dissolved in dichloromethane (20 mL). Propylamine (0.08 mL) (Scheme B, Compound **B7**; wherein R₁ is two substituents independently selected from hydrogen and *n*-propyl), sodium triacetoxy borohydride (0.32 grams) and acetic acid (2 drops) were added to the mixture which was then stirred for 18 hours. Aqueous sodium hydroxide (20 mL of 1N sol'n) was then added and the layers were separated. The organic layer was concentrated and column chromatographed (silica gel) using a mobile phase of dichloromethane-methanol 19:1 to give Compound 1. Mp 63.5-64.5 °C; MS 373 (MH⁺).
- 25

Using the procedure of Example 1 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	mp (°C)	MS (MH ⁺)
1a	4-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]- <i>N</i> -propyl-benzenemethanamine	63.5-64.5	373
2	3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]- <i>N</i> -(3-methylpropyl)-benzenemethanamine	86-88	387
3	3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]- <i>N</i> -cyclopentyl-benzenemethanamine	94-94.5	399
4	3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]- <i>N</i> -cyclohexyl-benzenemethanamine	85-86	413
5	3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]- <i>N</i> -cyclopropyl-benzenemethanamine	80.5-81.5	371
6	<i>N</i> -[[3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]phenyl]methyl]-1-methyl-2-pyrrolidinemethanamine • (HCl) ₂	---	442
7	4-[2-[3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]phenyl]ethyl]-morpholine • (HCl) ₂	---	444
8	4-(4-chlorophenyl)-2-[[3-[(5-methyl-2-furanyl)methyl]phenoxy]methyl]-thiazole	83-84.5	425
9	<i>N</i> -[[3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]phenyl]methyl]-5-methoxy-1 <i>H</i> -indole-3-ethanamine • HCl	---	504
10	4-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]- <i>N</i> -cyclopentyl-benzenemethanamine	125.5-126.5	399

Example 2

5 3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]- benzenemethanamine (Compound 11)

Following the protocol of Scheme C, the thiazole compound prepared in Example 1 (2.20 grams) (Scheme B, Compound **B6**, wherein R₂ is chloro) was dissolved in ethanol (100 mL). Sodium borohydride (0.25 grams) was added to the mixture

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which was then stirred at ambient temperature for 4 hours before being quenched with aqueous ammonium chloride. The product was extracted with dichloromethane to give a 3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]phenylmethyl alcohol (See Scheme C, Compound **C1**). Mp 141-142.5 °C; MS 332 (MH⁺);

5 ¹HNMR (DMSO) δ 8.24 (s, 1H), 5.50 (s, 2H), 4.48 (d, 2H).

The phenylmethylalcohol compound (1.98 grams) (Scheme C, Compound **C1**) was dissolved in tetrahydrofuran (100 mL). Triphenylphosphine (1.84 grams), phthalimide (1.03 grams) and diethylazodicarboxylate (1.10 mL) were added to the mixture which was then stirred for 16 hours before being evaporated in vacuo.

10 The residue was column chromatographed (silica gel) using a mobile phase of hexane-ethyl acetate 2:1 to give a N-[3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]phenylmethyl]phthalimide (Scheme C, Compound **C2**). Mp 156.5-157.5 °C; MS 461 (MH⁺).

The phthalimide compound (1.65 grams) (Scheme C, Compound **C2**) was
15 suspended in ethanol (100 mL). Hydrazine hydrate (1 mL) was added and the reaction was stirred at reflux for 2 hours before being cooled to ambient temperature. The mix was then filtered and the filtrate was evaporated. The crude solid was dissolved in dichloromethane, then sequentially washed with 1N
20 potassium hydroxide and water. The organic layer was then evaporated to give 3-[[4-(4-chlorophenyl)-2-thiazolyl]methoxy]benzenemethanamine Compound **11**. Mp 117-118.5 °C; MS 331 (MH⁺); ¹HNMR (CDCl₃) δ 7.85 (d, 2H), 7.50 (s, 1H), 7.40 (d, 2H), 5.43 (s, 2H), 3.86 (s, 2H).

Biological Examples

The compounds of the present invention are useful as inhibitors of a nicotinamide
25 adenine dinucleotide oxidase hydride donor. The following biological examples demonstrate the use of the instant compounds in a method for treating or ameliorating a reactive oxygen species mediated disease.

Example 1

Oxidase Inhibition Assay

- Whole cells (human neutrophils) are incubated with a pro-inflammatory agonist phorbol myristate acetate (PMA) in the presence or absence of test compound to
- 5 measure the superoxide-mediated reduction of Cytochrome c at 550 nm.
- Inhibition of the oxidase is determined by a decreased absorbance at 550 nm, in response to test compound, relative to the absorbance seen with a vehicle control.

Method

- 10 The buffy coat from one unit of blood is split evenly into four 50 mL tubes. To each tube 30 mL 3% Dextran (in 0.9% NaCl) is added and the tubes are inverted to mix. Tubes are allowed to sit undisturbed for 25 minutes. The resulting supernatant is recovered into four fresh tubes and centrifuged for 10 minutes at 600 X g, 4°C. The supernatant is discarded and pellets are resuspended in 35 mL
- 15 0.9% saline. 10 mL Ficoll-Paque PLUS (Pharmacia Biotech AB) is layered beneath the cell suspension and centrifuged at 600 X g for 40 minutes at room temperature. The supernatant is again discarded and tubes are tapped to loosen the resulting pellets. 20 mL 0.2% ice cold saline is added for 30 seconds followed by 20 mL 1.6% ice cold saline to lyse the remaining erythrocytes in the pellets.
- 20 The pellets are centrifuged for 10 minutes at 600 X g, 4°C, and the supernatant is discarded. The neutrophil pellets are resuspended in HBSS-glucose buffer (1mg/mL), adding 2.5 mL to each tube for a total volume of 10 mL. The cell suspension is then counted on a hemocytometer.
- 25 The cell suspension is diluted to a concentration of 5×10^6 /mL in HBSS-glucose and treated with 1 μ g/mL Cytochalasin B (5 mg/mL DMSO) for 10 minutes at 37°C in a shaking water bath. Cells are diluted to 6×10^5 cells/mL in 92 μ M Cytochrome c for a final concentration of 5×10^4 cells/well.

The NADPH-oxidase assay is run on a Biomek 2000 workstation. The workstation adds 2.5 μ L compound per well from source plates plus 12.5 μ L per well 4 μ M PMA (agonist). This volume is brought up to 100 μ L total per well in the assay plates upon the addition of the prepared cells (85 μ L). The final concentration of drug is 25 μ M and PMA is 0.5 μ M under these conditions.

The QC curve is a dose-response curve (from about 31.25 nM to about 4000 nM) for competitive binding against a known oxidase inhibitor such as DPI (diphenylene iodonium chloride). The following format was used for each compound tested:

Wells	% Inhibition	Inhibitor	Agent added
A-D	Control wells	2.5 μ L vehicle	12.5 μ L (agonist)
E-F	Blank wells	2.5 μ L vehicle	12.5 μ L (HBSS)
G-H	~70% (at 250 nm)	2.5 μ L of 10 μ M DPI	12.5 μ L (agonist)

The plates are incubated for 1 hour at 37°C without CO₂. The plates are then incubated at room temperature for 30 minutes and the absorbance is read at 550 nm. The data for instant compounds of the invention is shown in Table 1.

Table 1

Cpd	IC ₅₀ (μ M)
1	1.65
2	2.5
3	0.04
4	0.13
5	3.45
6	10
7	1.47
8	0.7

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Cpd	IC₅₀ (μM)
9	0.3
10	0.7
11	1.9

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the

5 following claims and their equivalents.